IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	: 1648	**Customer No.: 035811**
Examiner	: Emily M. Le	
Serial No.	: 10/600,361	
Filed	: June 20, 2003	Docket No.: 1187-R-02
Applicants	: Jean-Marie Andrieu	
	: Louis Lu	
Title	: METHODS, AND COMPOSITIONS	Confirmation No.: 7112
	: FOR A THERAPEUTIC ANTIGEN	
	: PRESENTING CELL VACCINE	
	: FOR TREATMENT OF	
	: IMMUNODEFICIENCY VIRUS	
		Dated: March 4, 2009

RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the Official Action dated December 19, 2008.

Claims 44 and 52-56 are pending. Claims 44 and 52-56 are rejected.

Claim 44 is rejected as obvious under 35 USC §103(a) over US '177.

Claim 44 is not obvious under 35 USC §103(a) over US '177. Reasons are set forth below.

First, US '177 fails to teach all the elements of Claims 44 and 52-56. This is because US '177 does not teach a composition comprising an "autologous virus" that "is isolated from the blood tissue of a patient" as required by the claims. In fact, the rejection admits that "[w]hile the dendritic cells used by Belardelli et al. [(US '177)] are autologous, it is not readily apparent if the virus used by Belardelli et al. is also autologous." This is true because the virus used in US '177 is not an autologous virus.

It is also apparent from an examination of the *in vitro* experiments described in US '177 that the virus used in these experiments is not an autologous virus. The rejection states that US '177 teaches a composition comprising dendritic cells pulsed with inactivated HIV and a pharmaceutically acceptable carrier, and cites paragraphs [0066]-[0067] and [0071] of US '177

in support. However, these paragraphs never mention the origin of the virus and it is absolutely clear the virus used in US '177 is not an autologous virus.

Indeed, US '177 uses the SF162 strain of the HIV virus for evaluating the primary response to HIV antigens elicited by IFN-DCs *in vitro* and DCs that are derived from monocytes obtained from blood donors. *See e.g.* US '177 at paragraphs [0118] and [0164] (stating "Autologous PBLs were stimulated with DCs pulsed with AT-2 inactivated HIV-1. HIV-1 SF162 strain was inactivated by AT-2 and stored at -140°C. until use.").

Importantly, the SF162 strain was produced from HIV isolates recovered from the spinal fluid of an unknown patient in the late 1980's which has been propagated in laboratories throughout the world since then. *See e.g* Cheng *et al.* 86 Proc. Natl. Acad. Sci. USA 8587 (1989) (describing isolation and propagation of SF162) (courtesy copy attached). This means it is absolutely clear from Cheng that the HIV-1 SF162 virus used in US '177 is not "an autologous virus isolated from the blood tissue" of the individual patient to be treated with the dendritic cells loaded with this AT-2 inactivated virus as required by the claims. Instead, the virus in US '177 is a non-autologous virus isolated from blood free, cerebrospinal fluid (CSF). Stated differently, the virus used in the *in vitro* experimentations of US '177 is not an autologous virus.

It is also apparent from an examination of the *in vivo* experiments described in US '177 that the virus used in these experiments is not an autologous virus. The *in vivo* experiments in US '177 use a SCID (Severe Combined ImmunoDeficiency) mouse model in which the immune system was "reconstituted" using human PBLs to evaluate the primary antibody response to HIV antigens elicited by IFN-DCs. *See* US '177 at paragraph [0169]. US '177 also states that "recent data have suggested that a human primary immune response can be generated in hu-PBL-SCID mice, especially when the chimeras are injected with antigen pulsed DCs" and cites Santini *et al.* (191 J. Exp. Med. 1777 (2000)) in support of this statement. *See* US '177 at paragraph [0169].

The Applicants note that, in fact, Santini is their own published scientific article with disclosure corresponding to US '177. *See* Santini (note authors, subject matter of the article, experimentation, and figures especially Figs. 1C, 3B, 3C, 5, 6 and 7b).

This also means the "Material and Methods" disclosed in Santini correspond to the experimental conditions of US '177. Importantly, Santini teaches that the virus used for inducing a primary response to HIV-1 antigens in hu-PBLs model is HIV-1 SF162 strain inactivated by AT-2 (*see* Santini et al., p. 1779, left column, "Induction of Primary Response to HIV-1 Antigens and Proliferation Assay"). Thus, given that paragraph [0170] of US '177

corresponds to the paragraph at page 1779, left column in Santini entitled "Induction of Primary Response to HIV-1 Antigens and Proliferation Assay[,]" it is clear that US '177 used the SF162 HIV strain to induce the primary response to HIV-1.

This use of the SF162 HIV strain in the *in vivo* experiments of US '177 is also confirmed by the fact that in US '177 the effective neutralization of HIV-1 infection in activated human PBL *in vitro* is confirmed using the combined sera of hu-PBL-SCID mice receiving 10 $TCID_{50}$ of HIV-1 SF162 strain which was added to PHA activated PBMC.

Clearly, the virus used in US '177 has been propagated in the laboratory since 1989 and is thus not a wild-type virus and no longer has the features of a wild-type human virus. This virus also is not an autologous virus because the PBLs injected in SCID mice are from human donors.

Furthermore, the Applicants are certain no autologous virus (*i.e.* virus from the PBLs provided by human donors) was injected into the mice in US '177. This is because in US '177 all the donors are healthy donors, meaning that they have never been infected by HIV and were screened for HIV-1 and hepatitis before PBL donation. *See e.g.* US '177 at paragraph [0170] and Santini at 1779, last paragraph. Thus, it is totally clear that the PBLs, and consequently DCs of the human donors in US '177, have never been in contact with autologous virus.

Additionally, the Applicants would like clarify that the term "autologous" with regard to the human immunodeficiency virus (HIV), such as in the claims, only refers to the particular HIV virions infecting an individual human patient. This means the concept of autology is totally irrelevant with regard to US '177 and the mouse model described therein.

Second, the experiments of US '177 are irrelevant to solving the problem addressed by the claimed pharmaceutical compositions. The rejection states that "[h]owever, due to the many variability in the many type of HIV isolates and the ability of the virus to mutate, it would have been *prima facie* obvious for one of ordinary skill in the art, at the time the invention was made, to use autologous HIV[.]" The Applicants disagree as this is mere speculation.

The Applicants would like to point out that the object of US '177 is to find a process for deriving dendritic cells (DCs) from mononuclear cells in culture after which DCs obtained may be used to make a vaccine. Thus, the optimization in US '177 is focused on the process of preparing the DCs, and not on the virus used to pulse the DCs. For this reason, one of ordinary skill in the art would not be motivated, based on US '177, to modify the virus as the Applicants have, but would instead merely be motivated to modify the process for obtaining the DCs.

Furthermore, the animal model used in US '177 makes it impossible for one of ordinary skill in the art to see any advantage in trying to replace the non-autologous virus of US '177 with an autologous virus. Consequently, one of ordinary skill in the art would not be motivated to modify the virus used in US '177.

Third, the Applicants would also like to explain, more particularly, why the animal model used in US '177 would not motivate one of ordinary skill in the art to replace a non-autologous virus with an autologous virus. As explain above, the virus used in US '177 is a non-autologous virus. Furthermore, US '177 stipulates that the PBLs donors are healthy donors (meaning that they have never been infected by HIV), and were screened for HIV-1 and hepatitis before donation. This excludes the use of autologous virus. This double-checking procedure is to be sure that the HIV-1 in US '177 is not the HIV from the donor (*i.e.* an autologous virus). Thus, US '177 teaches away from the use an autologous virus.

This means that one of ordinary skill in the art would not be motivated, on the basis of US '177, to modify the model disclosed therein and arrive at the claimed pharmaceutical compositions. This is especially true given that US '177 arguably teaches away from any such modification. Stated differently, this means the "variability in the many type[s] of HIV isolates and the ability of the virus to mutate" referred to in the rejection is totally irrelevant to the obviousness of the claimed pharmaceutical compositions.

Fourth, the teachings of US '177 cannot be extrapolated to autologous virus. The rejection states that one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for using autologous HIV because the use of autologous antigens are routinely practiced in the art.

The Applicants respectfully disagree. This is because US '177 cannot be extrapolated to a human system, and thus to autologous virus for several different reasons. One reason is US '177 shows that injection of IFN-treated HIV-1-pulsed DCs into SCID mice reconstituted with PBLs results in the generation of a potent primary immune response, as evaluated by the detection of human antibodies to various HIV-1 antigens. Another reason is that US '177 shows, in its animal model, that antibodies such as the anti-gp41, anti-gp160, anti-gp120 and anti-p24 antibodies are produced. *See* US '177 at paragraph [0106]. However, in humans, there is no production of anti-gp41 antibodies during HIV-1 infection. Furthermore, the production of such antibodies is undesirable.

This is demonstrated by the article Lu *et al.* (10 Nature Medicine 1359 (2004)) which is based on the disclosure in the Applicants' patent application. *See* Lu (courtesy copy attached). In Lu, the Applicants published experimental data from the therapeutic vaccination of 18 chronically HIV-1-infected and untreated individuals with autologous monocyte-derived DCs loaded with autologous AT-2 inactivated HIV-1. *See* Lu at 1359 (Abstract). The Lu article clearly states that "[c]onsidering the humoral arm of the immune response after vaccination, it is interesting to observe that our inactivated whole HIV-1-loaded DC vaccine did not induce any neutralizing antibodies." *See* Lu at 1362. Lu also shows the total titers of antibody to HIV-1 remained unchanged following therapeutic vaccination. *See e.g.* Lu at 1361.

Altogether, Lu shows that one of ordinary skill in the art would not have had a reasonable expection of successfully using autologous HIV in view of the experimental data provided by US '177.

Fifth, one of ordinary skill in the art would not have had a reasonable expectation of successfully using autologous HIV virus given the teachings of US '177 because US '177 teaches that partially mature DCs can only be obtained after a single step treatment that requires type I IFN as an essential factor. *See* US '177 at paragraph [0024]. Furthermore, in US '177 the mature DCs obtained are described as IFNγ-producing cells. *See e.g.* US '177 at paragraphs [0069] and [0071].

In contrast, Lu states that "only 10% of gag-tetramer-staining $CD8^+$ T cells have been reported to express IFN-γ following gag-specific stimulation..., it seems that more than 90% ([5.3% - 0.35%] ÷ 5.3% = 93.4%) of HIV-1 specific memory $CD8^+$ T cells expanded by the inactivated whole virus-pulsed DCs could probably be attributed to HIV-1 antigenic determinants other than gag." *See* Lu at 1363.

Thus, Lu shows that IFNγ is a poor surrogate marker for the killing of HIV which contradicts the teachings of US '177. Altogether, this makes it clear that one of ordinary skill in the art would not have a reasonable expectation of successfully using autologous virus in combination with the teachings of US '177.

The Applicants agree when the rejection states that, in the context of anticipation rejections, the recitation of a new use, new function or unknown property which is necessarily inherently present in the prior art does not make a claim patentable. However, the current rejections are obviousness rejections and it is self evident to state:

> That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.

See In re Spormann and Heinke, 150 U.S.P.Q. 499, 452 (CCPA 1996) (emphasis added). Moreover, the Applicants are claiming a completely new pharmaceutical composition and not just some new function of a "known material" that was identified and characterized in the prior art. This is because the prior art does not describe, nor suggest, the claimed compositions. Thus, the Applicants entirely disagree with the statement in the rejection that "the composition of Belardelli et al. is the claimed composition" for the reason set forth above.

Claims 52-56 are rejected as obvious under 35 USC §103(a) over the combination of US '177 and Lu.

Claims 52-56 are not obvious under 35 USC §103(a) as being unpatentable over the combination of US '177 and Lu. This is because the claimed pharmaceutical compositions comprising autologous dendritic cells and autologous HIV virus are non-obvious over US '177, as explained above, such that the same compositions comprising an adjuvant are also non-obvious and patentable over the combination of US '177 and Lu. Stated differently, Lu does nothing to cure the deficiencies of US '177 as discussed above.

The Applicants respectfully request withdrawal of the rejections made under 35 USC §103(a).

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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